Remarks

The present invention provides methods for inducing apoptosis of a selected group of vertebrate cells, e.g., a tumor, *in vivo*, by administering a non-pathogenic bacterium comprising a recombinant nucleic acid molecule encoding a thiaminase targeted to said selected group of vertebrate cells, whereby the level of thiamin in the cells is reduced sufficiently to induce apoptosis.

By the present communication, Claims 18, 25, 27, and 32 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as described herein as the amendments are fully supported by the specification as filed. Claims 1 and 3 have been cancelled without prejudice. Amendments submitted herewith are not to be construed as a dedication of the subject matter not presently claimed to the public. Applicants reserve the right to pursue claims as originally filed in a continuation application.

The amendments provided herewith present fewer claims for consideration, and are submitted to place the present application in condition for allowance, or at a minimum, in better condition for appeal. Accordingly, entry of the amendments provided herewith is submitted to be proper and is respectfully requested.. See MPEP § 714.12.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented in the **Listing of Claims** commencing on page 2, with an appropriate defined status identifier. Claims 10-11, 16-26, and 32 are pending, with claims 16, 17, and 20-24 withdrawn as being drawn to non-elected matter, and claims 10-11, 18-19, and 25-27, and 32 under active consideration. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Provisional Double Patenting Rejection: Claims 1, 3, 10, 11, and 25-27.

The provisional rejection of claims 1, 3, 10, 11, and 25-27 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-7, and 15-20 of copending U.S. App. No. 10/342,119, is acknowledged. This issue will be addressed in due course pending resolution of all other issues in the case, e.g., by submission of a suitable Terminal Disclaimer or other action as may be appropriate pending indication of allowance in both cases.

Rejection under 35 U.S.C. § 112, first paragraph: Claims 1, 3, 25-27, and 32

The rejection of Claims 1, 3, 25-27, and 32 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is respectfully traversed. This is alleged to be a new matter rejection.

Initially, the rejection as to Claims 1 and 3 is rendered moot by the cancellation thereof by the present communication. Claims 25-27 and 32, as amended, require avirulent *C. sporogenes* ATCC 8075, support for which is found in the specification at, for example, page 36, line 21, avirulent *C. beijerinckii*, support for which is found in the specification at page 36, line 12, or attenuated non-pathogenic *S. typhimurium*, support for which is found in the specification at page 34, lines 25-29. Methods of rendering these bacteria avirulent or attenuated are found in the specification. For example, one of skill in the art would know that avirulent *C. sporogenes* ATCC 8075 is discussed by Kobayashi (*Vitamins* 1975, **49**:45-51,) reference to which is provided in the specification at page 36, line 22. Furthermore, one of skill in the art would know that reference to Minton et al. 1995 (specification page 36, line 13) refers to Minton et al. (*FEMS Microbiol Rev.* 1995 Oct;17(3):357-64) which provides a description of the introduction of nitroreductase into a clostridial expression vector and introduction of the resultant plasmid into *C. beijerinckii*. Finally, one of skill in the art would know that discussion and methods of

production of attenuated non-pathogenic S. *typhimurium* for cancer therapy is found in Low *et al.*, 1999 (*Nature Biotech.* 17:37-41,) Pawelek *et al.*, (*Cancer Res.* 57:4537-4544) and Salzman *et al.*, 1997 (*J. Pediatr. Surg.* 32:301-306.)

Thus, the requirements of Claims 25-27, and 32 regarding avirulent *C. sporogenes* ATCC 8075, avirulent *C. beijerinckii*, or attenuated non-pathogenic *S. typhimurium*, find support in the specification and thus do not constitute new matter. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (Written Description): Claims 18-19

The rejection of Claims 18-19 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description, is respectfully traversed. The Examiner asserts (Office Action mailed 1/25/2006, page 6, paragraph 2, lines 3-6) that the elements of the combination "both 90% identical to an equal length of at least 200 nucleotides" are not named together, and hence the combination lacks written description.

Initially, the Examiner's attention is directed to the specification at page 40, lines 13-16, wherein the following statement is made:

> In addition, where features or aspect of the invention are described in terms of Markush groups or other grouping of alternatives, those skill in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Accordingly, it is understood that Markush and other groupings of alternatives used in the specification contemplate each member of such groups individually.

Furthermore, express support for Claims 18-19, as amended, is found in the specification at page 11, lines 21-25:

> The invention also provides an isolated, purified, or enriched nucleic acid molecule that has a nucleotide sequence at least 90% identical, preferably at least 95%, 97%, 98%, 99%, or 100% to a portion of a *Naegleria gruberi* thiaminase gene or coding sequence at least 15, 17, 20, 25, 30, 35, 40, 50, 75, 100, 200, or even more nucleotides in length.

Accordingly, in view of the use of Markush and other groupings in the specification, as discussed on page 40, lines 13-16, each of the 6 percentages recited immediately above is specifically associated with each of the 12 nucleotide lengths recited immediately above. Thus, explicit support for the combination recited in Claim 18 (i.e., 90% and 200 nucleotides) is found in the specification.

Furthermore, Claim 18, as amended, recites language expressly found in the specification at, for example, page 11, lines 21-25; *viz*,

> ... a portion of the N. gruberi thiaminase sequence of SEQ ID NO. 3 at least 200 nucleotides in length.

Accordingly, reconsideration and withdrawal of the current rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (Enablement): Claims 1, 3, 11, 25-27, and 32

The rejection of Claims 1, 3, 11, 25-27, and 32 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, is respectfully traversed for at least the reasons of record.

Initially, the rejection as to Claims 1 and 3 is rendered moot by the cancellation thereof by the present communication. Concerning Claims 11, 25-27, and 32, Applicants gratefully acknowledge the Examiner's indication (Office Action mailed 1/25/2006, page 7, paragraphs 1-4) that the specification is enabling for the following elements; *viz*,

> ... the specification, while being enabling for
> 1. SEQ ID NO: 3, which encodes thiaminase I from *Naegleria gruberi*, vectors containing a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi* operatively linked to a promoter,
> 2. cells transformed in vitro by said vector, and
> 3. bacterium selected from the group consisting of non-pathogenic attenuated *C. sporogenes, C. beijerinckii* and *S. typhimurium* comprising a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi*.

However, the Examiner's attention is directed to the following assertion (Office Action mailed 1/25/2006, page 5, paragraph 5, lines 1-3) which alleges non-enablement for Claims 1, 3, 11, 25-27, and 32:

> The specification does not reasonably provide enablement for the breadth of the claims, which are directed to *in vivo* methods of inducing apoptosis by administration to a selected group of vertebrate cells, ... (emphasis added)

It is submitted that the current rejection as to Claims 11, 25-27, and 32 is improper because these claims do not provide a method of inducing apoptosis as asserted by the Examiner in the Office Action mailed 1/25/2006, at page 1, paragraph 5, lines 1-3. Indeed, Claim 11 provides a vector comprising a recombinant nucleic acid sequence encoding thiaminase I from *N. gruberi*, which has been indicated as enabled. Furthermore, Claim 25 and dependent Claims 26-27 and 32 are directed to bacteria comprising a recombinant nucleic acid sequence encoding thiaminase I from *N. gruberi*, which has been indicated as being enabled. Accordingly, reconsideration and withdrawal of the current rejection is requested.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. In the event that any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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